A 52-year-old woman with history of generalized anxiety disorder and perimenopausal hot flashes presented to the emergency department with 3 days of subjective fever, diaphoresis, and right upper quadrant abdominal pain. She described the pain as sharp, intermittent, and radiating across her upper abdomen with no relieving factors. She reported intermittent dyspnea and palpitations over the past several months, but denied any chest pain, nausea, or vomiting. She consumed alcohol rarely and never used tobacco or illicit drugs. Her medications included St John’s Wort for anxiety and clonidine 0.1 mg twice daily for hot flashes. Her family history was unremarkable.

Upon arrival to the emergency department, she was afebrile with blood pressure 190/100 mm Hg, heart rate 86 beats/min, and oxygen saturation 97% on room air. Physical examination revealed a diaphoretic female with mild right upper quadrant abdominal tenderness to deep palpation with no rebound, guarding, masses, or organomegaly. Cardiac exam revealed a regular rhythm without murmurs and no jugular venous pressure elevation. Lung fields were clear. Laboratory testing demonstrated the following (reference ranges provided parenthetically): hemoglobin 14.0 g/dL (12.0 to 15.5 g/dL), leukocyte count 27.3 white blood cells/L (3.4 to 9.6×10⁹), creatinine 0.95 mg/dL (0.84 to 1.21 mg/dL), aspartate aminotransferase 32 U/L (8 to 48 U/L), alanine aminotransferase 20 U/L (7 to 55), alkaline phosphatase 73 U/L (40 to 129 U/L), total bilirubin 0.6 mg/dL (<1.2 mg/dL), sensitive thyroid stimulating hormone 0.9 mIU/L (0.3 to 4.2 mIU/L), lactate 4.8 mmol/L (0.5 to 2.2 mmol/L), baseline troponin T 0.72 ng/mL (<0.01 ng/mL), and N-terminal pro-B-type natriuretic peptide 20,800 pg/mL (<152). Chest x-ray revealed bilateral hazy opacities. Electrocardiogram showed sinus rhythm with nonspecific T-wave changes.

1. Which one of the following diagnoses is most consistent with the patient’s clinical picture?
   a. Acute cholecystitis
   b. Pulmonary embolism
   c. Community-acquired pneumonia
   d. Hypertensive emergency
   e. Acute coronary syndrome

Acute cholecystitis is a reasonable consideration in this patient with right upper quadrant abdominal pain and tenderness, leukocytosis, and subjective fever episodes, but this diagnosis is unlikely in a patient with normal hepatic function tests and would not account for the elevated troponin T or N-terminal pro-B-type natriuretic peptide levels. Whereas pulmonary emboli can cause heart strain and lead to elevated cardiac biomarkers, this patient denies chest pain and lacks a clinical history that would fit with this diagnosis. Moreover, pulmonary emboli causing heart strain would be more likely to cause hypotension. The presence of subjective fevers, leukocytosis, lactic acidosis and infiltrates on chest x-ray could be consistent with a diagnosis of community-acquired pneumonia but would not adequately explain the cardiac biomarker abnormalities.

Hypertensive emergency applies to patients with a systolic pressure greater than or equal to 180 mm Hg and/or diastolic pressure greater than or equal to 120 mm Hg with evidence of end-organ dysfunction, which in this case includes pulmonary edema and non-ST-elevation myocardial infarction.
Infarction (MI). Acute coronary syndrome is caused by acute atherosclerotic plaque rupture leading to myocardial ischemia and infarction (type 1 MI), whereas type 2 MI is caused by mismatch between oxygen supply and demand without acute atherosclerotic plaque rupture. Whereas coronary angiography may be needed to differentiate the two etiologies, this patient displays neither ischemic symptoms nor major atherosclerotic risk factors, making acute coronary syndrome less likely. Given her elevated troponin T in the setting of severe hypertension, type 2 MI secondary to hypertensive emergency is the more likely diagnosis.

Transthoracic echocardiogram revealed a left ventricular ejection fraction (LVEF) of 31% (50% to 55%) with regional wall motion abnormalities and grade 3/4 diastolic dysfunction. Cardiac catheterization demonstrated nonobstructive atherosclerosis with a left ventricular end-diastolic pressure of 32 mm Hg (14 to 24 mm Hg) and findings consistent with dilated cardiomyopathy. The patient continued to be hypertensive and was administered intravenous metoprolol for blood pressure control. She subsequently experienced worsening hypertension and sinus tachycardia. Her respiratory status deteriorated, and bedside echocardiogram revealed a worsening LVEF. She was intubated due to progressive respiratory distress. Computed tomography (CT) scan of the chest revealed pulmonary edema with possible alveolar infiltrates.

2. Which one of the following is the most likely condition that is driving this patient’s worsening clinical status after administration of metoprolol?
   a. Essential hypertension
   b. Coronary vasospasm
   c. Thyrotoxicosis
   d. Pheochromocytoma
   e. Stimulant intoxication

   Essential hypertension can lead to hypertensive emergency but would be expected to respond to intravenous beta blockers with an improvement in blood pressure rather than worsening hypertension. Coronary vasospasm can be induced by administration of beta blockers, especially in the setting of stimulant intoxication, and could explain the intermittent epigastric pain, elevated cardiac biomarkers, and worsening systolic function in the setting of nonobstructive coronary angiography. However, coronary vasospasm often produces ST-elevation on electrocardiogram during symptoms and would not explain the worsening hypertension that this patient experienced. Thyrotoxicosis is a consideration for a patient with accelerated hypertension but would be unlikely given her normal thyroid stimulating hormone level on admission. Furthermore, beta blockers would block the sympathetic effects of thyroid hormone and alleviate hypertension.

   Pheochromocytoma is a rare catecholamine-secreting adrenal tumor that can cause paroxysmal hypertension and hypertensive emergency. It should be suspected in patients with worsening hypertension after administration of selective beta-adrenergic receptor blockers, as these lead to unopposed alpha-adrenergic activity by the elevated catecholamine levels. Use of stimulants, such as cocaine or methamphetamine, can similarly cause hypertension after administration of beta blockers mimicking pheochromocytoma.

   Although stimulant abuse may be a more common cause of this clinical presentation among the general population, this was thought to be less likely in our patient with no history of substance abuse and a urine toxicity screen was not obtained. Her history of anxiety, hot flashes, dyspnea, and paroxysmal palpitations was more consistent with a diagnosis of pheochromocytoma. Patients with persistently high levels of circulating catecholamines can develop a stress cardiomyopathy, which can acutely worsen as the systemic vascular resistance increases. Stress cardiomyopathy can present with regional wall motion abnormalities on echocardiogram, although they are not typically in the distribution of a single coronary artery. This patient was thought to have
developed flash pulmonary edema as a result of the acute increase in afterload.

3. Which one of the following is the best initial test to evaluate a patient with suspected pheochromocytoma?
   a. Plasma or urine catecholamines
   b. Plasma or urine metanephrines
   c. Plasma or urine vanillylmandelic acid (VMA)
   d. Plasma or urine chromogranin A
   e. CT scan of abdomen and pelvis

Diagnosis of a suspected pheochromocytoma involves laboratory testing for evidence of excess catecholamines or imaging to identify the tumor. Laboratory testing can include concentrations of catecholamines (epinephrine, norepinephrine, or dopamine) or their metabolites (metanephrine, normetanephrine, VMA, or 3-methoxytyramine) in the plasma or urine. The Endocrine Society Clinical Practice Guidelines recommends initial screening with plasma free or 24-hour urinary fractionated metanephrines, as these appear to be the most sensitive tests. Certain medications can interfere with laboratory measurements and/or the degradation of catecholamines and result in falsely elevated metanephrine levels, including acetaminophen, mesalamine, labetalol, buspirone, and tricyclic antidepressants.

Chromogranin A is released with catecholamines in adrenal medullary and sympathetic neuronal vesicles and is sometimes used for patients with borderline or unclear results or as monitoring for recurrence. Imaging should not be obtained until there is biochemical evidence of a pheochromocytoma, as there is an increased likelihood of identifying asymptomatic, nonfunctioning incidentalomas. CT scan of the abdomen and pelvis is the preferred first-line imaging modality given its wide availability, low cost, and excellent visualization of the adrenal glands.

In this case, plasma free metanephrine was elevated to 55 nmol/L (<0.50 nmol/L). Subsequent testing for plasma catecholamines revealed levels that were above the maximum testing limit of the laboratory equipment, requiring dilution of the samples to obtain results. Diluted samples revealed elevated norepinephrine to 71,159 pg/mL (70 to 750 pg/mL), epinephrine to 48,015 pg/mL (≤111 pg/mL), and dopamine to 994 pg/mL (<30 pg/mL). Plasma chromogranin A was 6,246 ng/mL (<93 ng/mL). A CT scan of the abdomen and pelvis identified a large right adrenal heterogeneous mass with signs of recent hemorrhage.

4. Which one of the following medications is the best initial choice for preoperative management?
   a. Alpha blockers
   b. Beta blockers
   c. Calcium channel blockers (CCBs)
   d. Angiotensin-converting enzyme inhibitors
   e. Tyrosine hydroxylase inhibitors

The treatment of choice for pheochromocytoma is surgical resection, and an experienced endocrine surgeon should be involved once the diagnosis has been established. Anesthesia induction and surgical manipulation of the tumor can lead to dangerous abrupt increases in catecholamine levels, conferring a substantial perioperative risk to these patients. Preoperative medical management is essential, and surgery is typically delayed for 10 to 14 days for medical optimization to ensure adequate pharmacologic adrenergic receptor blockade in the event of intraoperative catecholamine surges. Several medication classes can diminish the effects of catecholamines and have been shown to be effective options in managing patients with functioning pheochromocytomas.

The most widely accepted approach involves a combination of alpha and beta blockade. Surging catecholamines lead to activation of alpha-adrenergic receptors, resulting in vasoconstriction, hypertension, and end-organ damage. Phenoxbenzamine, an irreversible nonselective alpha-1 and alpha-2 blocker, is the most commonly administered alpha-adrenergic medication due to its long half-life. Other options include reversible nonselective alpha blockers, such as phentolamine, or reversible selective alpha-1 blockers, such as prazosin.
terazosin, or doxazosin. Once adequate alpha-adrenergic blockade has been established, usually after 2 to 3 days, beta blockers should be added to reduce the tachycardia that is precipitated by the alpha blockade and prevent adverse cardiovascular effects of excessive beta-adrenergic stimulation by catecholamines. As seen in this case, beta blockers should not be used until alpha blockers have reached their full effects, otherwise the unopposed alpha-adrenergic stimulation will lead to worsening hypertension, vasoconstriction, and systolic dysfunction. The modest degree of alpha blockade provided by mixed alpha/beta blockers such as labetalol or carvedilol may not be adequate to prevent this effect.

CCBs inhibit calcium influx in vascular smooth muscle, thereby leading to direct arterial vasodilation. Both dihydropyridine and non-dihydropyridine calcium channel antagonists can be used when patients are persistently hypertensive or experiencing dose-limiting adverse effects from alpha blockers. There is no current evidence that angiotensin-converting enzyme inhibitors are useful as primary or adjunctive medications in the preoperative management of pheochromocytomas. Metyrosine, a tyrosine hydroxylase inhibitor, prevents further production of catecholamines and can be used to augment blood pressure control. It is particularly useful for patients with high catecholamine levels but its use is limited by its cost.

In this case, the patient initially displayed hemodynamic evidence of normotensive cardiogenic shock, which responded to intravenous milrinone and clevidipine. Phenoxybenzamine was started the day after diagnosis and propranolol, a nonselective beta-adrenergic receptor blocker, was added 2 days later. Metyrosine was subsequently added to reduce catecholamine biosynthesis before surgery. Phenoxybenzamine was transitioned to doxazosin upon discharge. The patient underwent right adrenalectomy 20 days after diagnosis and pathology confirmed pheochromocytoma. She tolerated the surgery without any major complications and was discharged on postoperative day 3.

5. Which one of the following statements is true regarding post-discharge follow-up for this patient?

a. Genetic testing is not indicated
b. She requires annual biochemical screening for recurrence
c. She should have repeat abdominal CT or positron-emission tomography—CT scan in 1 year
d. Her cardiomyopathy is likely irreversible
e. She will likely require long-term anti-hypertensive therapy

Recent advances in genetic testing have enhanced our ability to detect mutations in patients with pheochromocytomas. Contrary to the popular “10% rule” that is commonly taught to physicians (that pheochromocytomas are 10% familial, 10% malignant, and 10% extra-adrenal), approximately 30% of tumors have a known genetic basis. Identifying these mutations provides valuable prognostic information about the risk of recurrence and metastasis, as well as the need for screening in family members.

All patients need to be monitored for recurrence following surgical resection. The current recommendations include repeat biomarker testing 2 to 6 weeks after surgery followed by yearly biomarker testing for 10 years. In high-risk patients, including those who are young, have large tumors, or high-risk genetic mutations, screening should be offered lifelong. Postoperative imaging is not typically recommended unless biomarkers remain elevated or there is concern for metastatic disease at the time of presentation.

Patients with pheochromocytomas are at an elevated risk of myocardial injury and some can develop a catecholamine-induced cardiomyopathy. The majority will experience improved cardiac function as the circulating catecholamine levels normalize. Repeat echocardiograms are necessary to ensure that cardiac function recovers appropriately. Hypertension typically resolves after removal of the pheochromocytoma, and some patients may develop hypotension secondary to adrenal insufficiency if adrenalectomy is performed.

This patient was referred for genetic testing but declined. Repeat biomarker
testing 8 weeks after surgery demonstrated normalization of serum metanephrines, 24-hour urinary metanephrines, and 24-hour urinary catecholamines. She will continue to have annual testing for the next 10 years. Repeat transthoracic echocardiogram 6 days after initiation of preoperative medical treatment demonstrated resolution of systolic and diastolic dysfunction with LVEF 55%, as well as resolution of previously seen regional wall motion abnormalities. She was weaned off antihypertensive therapy after surgery and was discharged on a propranolol taper.

**DISCUSSION**

Pheochromocytomas are rare catecholamine-producing neuroendocrine tumors that arise from adrenal medullary chromaffin cells. The clinical presentation is highly variable and typically includes nonspecific symptoms secondary to direct effects from catecholamines. The most common symptoms include “spells” with episodic headaches (60% to 90%), palpitations (50% to 70%), and diaphoresis (55% to 75%). When all three of these symptoms are present, the specificity has been shown to be upwards of 90%. Less common symptoms include anxiety (20% to 40%), hyperglycemia (40%), fatigue (25% to 40%), and paroxysmal hypertension (30%); hypertension may be sustained and resistant to therapy. The paroxysmal nature of these symptoms provides an important clue to this diagnosis. As the mass enlarges, patients can develop pain from the mass compressing on nearby structures.

Pheochromocytomas can be imminently life-threatening and all patients with a suspected diagnosis should undergo biochemical testing for this disease. The majority of pheochromocytomas produce at least one catecholamine and patients typically have elevated levels of epinephrine, norepinephrine, and/or dopamine. Epinephrine and norepinephrine are metabolized into metanephrine and normetanephrine, which are further metabolized into VMA. Dopamine is metabolized into 3-methoxytyramine. The Endocrine Society Clinical Practice Guidelines recommends initial testing for plasma free metanephrine or 24-hour urinary fractionated metanephrines, as these appear to have the greatest diagnostic sensitivity. Patients with borderline results may benefit from a clonidine suppression test to distinguish patients with increased sympathetic activity from those with underlying pheochromocytomas. In this test, patients are given oral clonidine and have a repeat plasma normetanephrine drawn 3 hours later. Clonidine, an alpha-2 antagonist, will suppress neuronal norepinephrine release in patients without an underlying pheochromocytoma but will not have this effect on patients with a tumor. In patients with confirmed biochemical abnormalities, imaging should be obtained to localize the tumor. A CT scan of the abdomen and pelvis with and without intravenous contrast is the initial modality of choice, as the majority of pheochromocytomas are located within the abdomen and pelvis. In patients with adrenal tumors greater than 5 cm or concern for metastatic disease, further imaging with 123I-metaiodobenzylguanidine, magnetic resonance imaging, or positron-emission tomography—CT scans may be warranted.

Patients with pheochromocytomas can develop cardiovascular complications secondary to toxic effects of circulating catecholamines and acute cardiac disease is often the initial presentation. Pheochromocytomas can cause hypertension, cardiac arrhythmias, acute MI, left apical ventricular hypertrophy, and catecholamine-induced dilated cardiomyopathy with heart failure. When excessive catecholamine release produces peripheral vasoconstriction and reduced myocardial systolic function, a low-output state progressing to cardiogenic shock can occur. Many of these cardiovascular complications are reversible after the effects of catecholamines have been blunted, although the damage can be irreversible and close monitoring is necessary.

As exemplified in our case, the acute use of beta-adrenergic receptor blockers can be life-threatening in patients with pheochromocytomas. Even in severe cases, aggressive pharmacologic management should be
prioritized over early surgical resection because of the high mortality associated with catecholamine surges in a patient without adequate preoperative adrenergic blockade. The most common regimen for preoperative management includes alpha blockade followed by beta blockade. CCBs and metyrosine have a role as adjunctive medications.

Patients with confirmed pheochromocytomas require yearly physical exams, blood pressure measurements, and biochemical screening for at least 10 years after surgery to assess for recurrence. Genetic testing should be considered for all patients, as identification of mutations provides prognostic information regarding the likelihood of recurrence, metastases, and hereditability in family members. Familial syndromes with an increased risk of developing pheochromocytomas include multiple endocrine neoplasia (MEN) 2A syndrome, MEN 2B syndrome, von Hippel-Lindau disease, and neurofibromatosis type 1, among other rarer syndromes.

**CONCLUSION**
Pheochromocytomas are life-threatening catecholamine-secreting tumors that require prompt diagnosis and treatment. Patients often present with manifestations of acute cardiac disease, which can include catecholamine-induced cardiomyopathy. This case outlines the presentation, work-up, treatment, and follow-up of pheochromocytomas. It is imperative to avoid beta-blocker therapy until alpha blockade has been established in all suspected cases of pheochromocytoma.

**Potential Competing Interests:** The authors report no competing interests.

**REFERENCES**

**CORRECT ANSWERS:** 1. d. 2. d. 3. b. 4. a. 5. b